Ces jeunes malades ont bien répondu au régime médical habituel. On suggère que l'ulcère peptique soit inclus dans le diagnostic différentiel des douleurs abdominales chroniques chez les enfants, surtout si elles ne cadrent pas dans les maladies infantiles communes. Il est alors important de pratiquer un repas baryté. Les mêmes recommandations s'appliquent lorsqu'un appendice normal est enlevé chez un enfant se plaignant de douleurs abdominales. Cette méthode permettra de découvrir un plus grand nombre de cas d'ulcère peptique et grâce à un diagnostic précoce et à un traitement immédiat elle contribuera à diminuer le pourcentage des complications et des mortalités. La fréquence des ulcères peptiques sans complication chez les enfants doit être bien supérieure à ce que les travaux sur les malades hospitalisés avec complications nous permettent d'entrevoir.

SUSTAINED-RELEASE NICOTINIC ACID (Nicospan)* EFFECT ON (1) CHOLESTEROL LEVELS AND (2) LEUKOCYTES

P. O. O'REILLY, M.B., B.Ch.,†
North Battleford, Sask., and
M. J. CALLBECK, R.N.‡ and
A. HOFFER, Ph.D., M.D.,¶ *Saskatoon, Sask.*

INTRODUCTION

RECENT INVESTIGATIONS of the administration of nicotinic acid to humans have shown that nicotinic acid lowers serum cholesterol levels.[3, 4, 8, 9, 10] Altschul[1, 2] has also demonstrated that in rabbits, normal or artificially raised serum cholesterol levels can be lowered by large doses of nicotinic acid and the well-known experimental atherosclerosis inhibited. The minimum effective dose in humans is one gram three times a day, and doses up to six grams a day have been used. Hoffer, O'Reilly and Callbeck[6] in a recent study showed how specific the hypocholesterolæmic action of nicotinic acid is. Neither nicotinamide nor nicotinyl alcohol (Roniacol) is active. The question of safety of prolonged medication with 3 to 6 g. per day of nicotinic acid has been studied by Hoffer and Callbeck.[7] They found that following at least one year's continuous treatment with nicotinic acid no liver dysfunction or significant shift in leukocyte pattern occurred, indicating the safety of the medication.

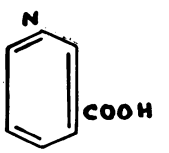
Of immediate concern are the side reactions which accompany the taking of the drug. They are: (a) The marked flushing and pruritus which occur in all cases. Associated with this, some persons report a numbness and weakness of the lower limbs and dizziness. Generally these reactions diminish and usually disappear after the first few days of treatment. However, some persons on prolonged medication report this reaction occurring sporadically throughout the treatment period. (b) Gastro-intestinal disturbances occur in a certain number of cases and may lead to interruption or discontinuation of the treatment. These gastric disturbances are believed by Altschul and Hoffer[5] to be due to the high acidity — that is, an unspecific factor — rather than to a specific action of nicotinic acid. They suggest that a solution of nicotinic acid buffered with $NaHCO_3$ and $KHCO_3$ may eliminate the gastro-intestinal disorders.

These side effects are possibly due to a very rapid absorption of nicotinic acid into the blood. We had earlier observed that after the intravenous administration of nicotinic acid there was a very marked vasodilatation. When the vasodilatation subsided, a short period of time followed during which the subject was refractory to further vasodilatation. In some instances no flush followed the taking of 2 g. of nicotinic acid orally, after the flush induced by 200 mg. of intravenous nicotinic acid had subsided. Furthermore, after some days of steady administration the vasodilatation tended to disappear. It thus seemed likely that the vasodilatation depended upon high serum levels of nicotinic acid and was independent of its hypocholesterolæmic effect. These findings suggested that adequate blood levels could be attained by some slow-release mechanism without producing a flush.

The purpose of this paper is to report on the action of a sustained-release form of nicotinic acid (Nicospan). The areas of investigation are: (a) the vasodilatation, (b) the effect on serum cholesterol levels, (c) the effect on leukocytes, (d) the side reactions.

Composition of Tablet

The structure formula of nicotinic acid may be represented as follows.



The sustained-release tablet (Nicospan) contains 500 mg. nicotinic acid in a special base which is liberated over a period of 7 to 11 hours after ingestion.

*Nicospan is the trademark of Wm. S. Merrell Company for its special nicotinic acid sustained-release tablet.

†Research co-ordinator and senior specialist, Saskatchewan Hospital, North Battleford, Sask.
‡Chief research psychiatric nurse, psychiatric research, Psychiatric Services Branch, University Hospital, Saskatoon, Sask.
¶Director, psychiatric research, Psychiatric Services Branch, University Hospital, Saskatoon, Sask.

TABLE I.—EFFECT OF NICOTINIC ACID (NICOSPAN) ON CHOLESTEROL LEVELS

Subject	Age	Sex	Weight	Cholesterol mg./100 ml. Initial	7 days	14 days
			Control			
1	40	F	120	246.4	234.0	250.8
2	40	F	90	300.2	243.2	213.1
3	48	F	170	342.0	283.3	286.6
4	56	F	128	261.8	249.6	243.2
5	47	F	113	240.6	228.0	220.5
6	39	F	113	269.5	248.9	249.9
7	36	F	185	291.2	258.8	245.1
8	87	F	84	261.8	263.3	263.3
9	64	F	263	227.1	231.8	238.8
10	45	F	133	231.0	253.5	281.2
Mean				267.16	249.44	249.31
			Nicospan			
1	67	F	246	294.5	177.1	179.4
2	61	F	175	344.5	217.5	210.6
3	66	F	136	273.6	177.1	161.8
4	64	F	169	223.2	120.7	101.4
5	21	F	101	201.4	124.7	Discontinued
6	31	F	92	245.5	194.2	205.9
7	41	F	111	212.8	119.7	Discontinued
8	27	F	103	245.8	161.0	Discontinued
9	39	F	165	372.4	229.4	269.5
10	45	F	155	224.2	132.8	134.7
Mean				263.79	165.42	180.5

A. VASODILATATION

In co-operation with Dr. T. Jones of the Wm. S. Merrell Company, we had previously examined experimental batches of slow-release nicotinic acid. The results were encouraging but vasodilatation still occurred much too frequently. However, after repeated experimentation one of us (A.H.) found that after the taking of one gram of the slow-release nicotinic acid preparation (Nicospan) no vasodilatation occurred. Fifteen volunteers were then persuaded to take one gram of this preparation. None of these volunteers had taken any form of nicotinic acid for several weeks before the trial, so that they were not tolerant to it. A single trial was considered sufficient, since the first dose of nicotinic acid itself produces the most severe and uncomfortable flush (the vasodilatation appears to be all or none). Three of the 15 volunteers reported slight flushing and 12 reported none; this indicated a major improvement in such a slow-release preparation.

B. CHOLESTEROL LEVELS

Trials with Nicospan were carried out on three patients over a seven-day period. The results obtained (mean decrease from 185 to 147 mg. %) indicated that the hypocholesterolæmic effect of Nicospan was as pronounced as with nicotinic acid itself. In view of these positive results a more extensive trial of the preparation was carried out at the Saskatchewan Hospital, North Battleford, by one of the authors (P.O. O'R.).

TABLE II.—MEANS AND STANDARD DEVIATIONS OF THE TREATED AND CONTROL GROUPS AT VARIOUS PERIODS

		N	Mean	S.D.
Before treatment	Treated group	10	263.79	54.41
	Control group	10	267.16	34.70
After one week	Treated group	10	165.42	37.14
	Control group	10	249.44	16.24
After two weeks	Treated group	7*	180.5	49.24
	Control group	10	249.31	22.02

(*N = 7 as 3 patients discontinued treatment).

Twenty female patients were selected, 10 for the control group and 10 for treatment. At the beginning of the experiment, the fasting total serum cholesterol was determined for each subject by the Schoenheimer-Sperry method. The subjects in the treated group were then given one gram of Nicospan three times daily for two weeks. The control group received no medication. Serum cholesterol levels were again determined one week and two weeks after medication was started.

TABLE III.—COMPARISON OF MEANS OF THE TREATED AND CONTROL GROUPS INDIVIDUALLY AT VARIOUS PERIODS

Treated group	D	t	P
Before treatment/after 1 week's treatment	98.37	4.43	<.01 Significant
Before treatment/after 2 weeks' treatment	102.20	3.37	<.01 Significant
Control group			
Before/after 1 week	17.72	1.48	<.20 >.10 Not significant
Before/after 2 weeks	17.85	1.32	<.30 >.20 Not significant

The two weeks of treatment are illustrated in Table I.

Statistical analysis of the data found in Table I is shown in Tables II, III and IV.

Subjects 5, 7 and 8 had to have the Nicospan discontinued because of side reactions. Table V illustrates cholesterol levels obtained.

TABLE IV.—COMPARISON OF MEANS OF THE TREATED AND CONTROL GROUPS AT VARIOUS PERIODS

	D	t	P	
Before treatment	3.37	0.11	.90	Not significant
After one week	84.02	6.10	.01	Significant
After two weeks	68.81	3.56	.01	Significant

TABLE V.—CHOLESTEROL LEVELS IN 3 SUBJECTS DISCONTINUING NICOSPAN

Subject	Cholesterol mg./100 ml. Initial	On Nicospan one week	Off Nicospan one week
5	201.4	124.7	223.6
7	212.8	119.7	213.6
8	245.8	161.0	207.9
Mean	220.0	135.13	215.03

TABLE VI.—EFFECT OF NICOTINIC ACID (NICOSPAN) ON LEUKOCYTES

	Before							1 week (Nicospan)							2 weeks (Nicospan)						
		Differential							Differential							Differential					
Subject	Total W.B.C.	Baso.	Poly.	Eos.	Lymph	Metamyelocytes	Mono.	Total W.B.C.	Baso.	Poly.	Eos.	Lymph.	Metamyelocytes	Mono.	Subject	Total W.B.C.	Baso	Poly.	Eos.	Lymph.	Metamyelocytes	Mono.
1	6200	—	59	1	37	1	2	7100	—	54	5	39	—	2	1	6500	2	51	4	38	—	5
2	4500	2	49	1	44	1	3	5900	—	37	1	57	1	4	2	4900	1	46	4	43	1	5
3	9100	1	69	2	28	—	—	8000	—	64	2	29	5	—	3	7200	—	57	1	40	—	2
4	7250	1	44	—	51	3	1	7300	—	56	—	38	3	3	4	7800	—	59	6	31	1	3
5	6500	—	35	4	59	—	1	5500	—	44	7	46	—	3								
															6	6800	—	58	3	38	—	3
7	7150	—	71	1	28	—	—	7400	3	63	—	32	—	2								
8	6850	1	56	3	38	—	2	7200	—	64	1	31	—	5								
9	10,000	—	67	1	29	1	2	12,000	3	61	—	34	—	2	9	13,400	1	70	5	19	3	2
10	8400	—	69	1	28	1	1	6500	—	50	3	44	2	1	10	7100	—	67	2	29	—	2

C. EFFECT ON LEUKOCYTES

The effect on leukocytes is shown in Table VI.

D. SIDE REACTIONS

(a) *Gastro-intestinal disturbances.*—These were marked in two cases and consisted of nausea, vomiting, diarrhœa and a feeling of general malaise. These reactions necessitated the discontinuation of medication after seven days' treatment. Two other patients felt nauseated throughout the treatment period.

(b) *Vasodilatation.*—Vasodilatation occurred in four cases. The flushing was less pronounced than that observed during previous nicotinic acid trials and did not last as long. It appeared on the second day of administration, lasted two days and then disappeared. In those cases where flushing did not occur, two subjects reported a tingling sensation in head and neck with a feeling of warmth.

(c) *Headache and a feeling of dizziness.*—During the first two days of medication three patients complained of these symptoms. However, they did not recur throughout the treatment period.

(d) *Hypotensive reaction.*—This reaction occurred in one patient on the sixth day of treatment, after which she felt nauseated and complained of general malaise; in view of this, treatment was discontinued.

DISCUSSION

Examination of Tables I-IV shows that Nicospan is a potent hypocholesterolæmic agent. Statistical analysis of the data presented in Table I showed no significant difference between the mean levels of the treated and control groups before the beginning of the experiment, but after one week's and two weeks' treatment the mean levels of the treated group dropped considerably. These mean levels were significantly differentiated at the 1% level of confidence both from the mean level before treatment (Table III) and from the mean levels of the control group for the same periods (Table IV). The mean levels in the control group remained relatively stable, and the differences noted could have arisen through chance factors (Table III). On these figures the efficacy of Nicospan in lowering cholesterol level is supported with a high degree of confidence, i.e., 1% level. The sustained-release form of nicotinic acid (Nicospan) is much more effective in lowering cholesterol levels than nicotinic acid *per se*. In our previous trials[8] it was found that, after one week of medication, nicotinic acid reduced cholesterol levels by 15%, whereas in this study a reduction of 37.4% was achieved after one week. This suggests that an adequate concentration of nicotinic acid must be maintained in the body throughout a 24-hour period in order to achieve a maximum effect. Table V illustrates the fact that the cholesterol returns to its initial level after discontinuation of the medication. After two weeks of medication, examination of the leukocyte count (Table VI) reveals a mild eosinophilia in six of seven cases. Hoffer and Callbeck[7] studied the effect of 30 days' treatment with nicotinic acid on leukocyte count and reported no significant shift in leukocytes. This suggests that the eosinophilia found in this study is not due to the specific action of nicotinic acid but, as Hoffer[11] suggests, may be due to an unspecific factor such as the plastic coating of the tablet. The vasodilatation which is so pronounced with administration of nicotinic acid is markedly reduced with the utilization of the sustained-release form (Nicospan). Six of the ten patients had no flushing and in those with flushing, the condition was not so marked as when nicotinic acid was administered. The gastro-intestinal symptoms may be due to high acidity, as postulated by Altschul and Hoffer,[5] or in view of the eosinophilia found, due to the plastic coating of the tablet. This last factor will be investigated. The one case of hypotensive reaction was accompanied by a marked vasodilatation, which suggests that this was the cause of the foregoing response.

SUMMARY

This study shows sustained-release nicotinic acid (Nicospan) to be much more effective in lowering cholesterol levels than nicotinic acid *per se*. After one week of administration Nicospan reduced cholesterol levels by 37.4%, as compared with 15% when nicotinic acid was given over the same period. Vasodilatation, which had occurred in all cases during previous nicotinic acid trial, did not appear in six cases. In those cases where it was present the flushing was not so pronounced. A mild eosinophilia was found in six of the seven cases given two weeks' medication. Gastro-intestinal disturbances occurred in four cases.

We wish to thank the following people who co-operated in the study: Dr. M. Podilsky, W. Hrychuk, Research Nurse, and Mrs. F. Taylor, B.A. The study was approved by the Saskatchewan Committee on Schizophrenic Research, and supported by the Department of National Health and Welfare, Ottawa, Canada. Nicospan was supplied by the Wm. S. Merrell Company.

REFERENCES

1. ALTSCHUL, R.: *Ztschr. Kreislaufforsch*, 45: 573, 1956.
2. *Idem*: *Circulation*, 14: 494, 1956.
3. ALTSCHUL, R., HOFFER, A. AND STEPHEN, J. D.: *Arch. Biochem.*, 54: 550, 1955.
4. ALTSCHUL, R. AND HOFFER, A.: *Ibid.*, 73: 420, 1958.
5. *Idem*: *Brit. M. J.*, 2: 713, 1958.
6. HOFFER, A., O'REILLY, P. O. AND CALLBECK, M. J.: Specificity of the hypocholesterolæmic activity of nicotinic acid. To be published.
7. HOFFER, A. AND CALLBECK, M. J.: Effect of nicotinic acid on leukocytes and liver function. To be published.
8. O'REILLY, P. O., DEMAY, M. AND KOTLOWSKI, K.: *A.M.A. Arch. Int. Med.*, 100: 797, 1957.
9. O'REILLY, P. O.: *Canad. M. A. J.*, 78: 402, 1958.
10. PARSONS, W. B. *et al.*: *Circulation*, 14: 495, 1956. *Idem*: *Proc. Staff Meet. Mayo Clin.*, 31: 377, 1956.
11. HOFFER, A.: Personal communication, 1958.

RÉSUMÉ

La vasodilatation qui accompagne l'administration d'acide nicotinique ne se manifeste que lorsque la concentration de ce produit dans le sang dépasse un certain niveau; elle n'a aucune portée sur l'abaissement de la cholestérolémie. Les auteurs ont employé une nouvelle forme de présentation où la vitamine est conjuguée avec une base spéciale (Nicospan, *marque déposée*) qui permet une libération lente du médicament, prolongée pendant sept à onze heures après l'ingestion. Ils ont pu ainsi dans la majorité des cas supprimer la congestion et la rougeur que plusieurs malades tolèrent mal. Non seulement observa-t-on un abaissement du cholestérol sanguin, mais encore dépassa-t-il celui que l'on obtient par l'administration de doses isolées d'acide nicotinique, rapidement absorbées. Deux malades recevant un gramme trois fois par jour accusèrent des nausées, des vomissements, de la diarrhée et une sensation généralisée de malaise. Ces phénomènes seraient attribuables à l'enrobement de substance plastique des comprimés. Une légère éosinophilie se manifesta chez certains autres.

Case Reports

MYOCARDIAL INFARCTION ASSOCIATED WITH HYPERCHOLESTEROLÆMIA IN A YOUNG EUNUCH*

H. Z. POMERANTZ, M.D., F.A.C.P. and N. SHEINER, M.D., *Montreal*

IT IS A WELL accepted fact in medicine that coronary atherosclerosis in persons under 40 is almost exclusively a disease of males.[1-3] Castration increases its incidence and severity in women,[4] while eunuchs are reported to show less atherosclerosis than normal men.[5-7] The high incidence of coronary artery disease in the male and the relative protection of the female have been attributed in large measure to the influence of the gonadal hormones on the distribution of lipids and lipoproteins considered to be etiologically related to atherosclerosis.[8-12]

It is therefore of interest to report the occurrence of myocardial infarction in a young male eunuch with hypercholesterolæmia, and to analyze the significance of such an event with a view to integrating this information with the currently held views outlined above.

A 36-year-old white man was admitted to the Jewish General Hospital because of severe epigastric and retrosternal pain of several hours' duration, associated with sweating and marked restlessness. Nine months earlier he had spent five weeks in another hospital with similar complaints, and a diagnosis of myocardial infarction and duodenal ulcer had been made.

The patient had undescended testicles, and surgical descent of the testicles had been attempted bilaterally at the Michael Reese Hospital in Chicago at the age of 13. The report from there indicated "absent right testicle, small atrophic left testicle brought down into the scrotum."

Ten years previously, at the age of 26, he had started treatment with testosterone both by injection and by subcutaneous implantation of pellets. Treatment was intermittent. He did not start to shave at all until testosterone therapy was started, and at present he shaves only once or twice weekly.

Family history.—The only member of his family of whom the patient had knowledge was his father, who was living in Chicago, in good health so far as the patient knew.

Physical examination.—His height was 68 inches (172.7 cm.) and his arm span 75 inches (190.5 cm.). There were scanty hair on his face and a female distribution of pubic hair and fat (Figs. 1 and 2). No testes could be found in the scrotal sac.

The blood pressure was 148/105 mm. Hg but soon fell to 100/70 mm. and maintained itself at this level except for a brief dip to 90/60 mm. The lung fields were clear, the heart rhythm was regular, and the sounds were normal. The liver edge was down 1-2 fingers' breadths below the costal margin.

Laboratory Data

The hæmoglobin value on admission was 74% with a hæmatocrit of 37%; one week later the hæmatocrit had become 41% without any specific therapy. White blood cells were 8400 per c.mm.; differential 67% neutrophils, 23% lymphocytes, 5% monocytes and 5% eosinophils. Stools were negative for occult blood. Urine was acid, with a specific gravity of 1.040; it was negative for sugar and showed 1-plus albumin; there were 5-8 red blood cells, 3-6 white blood cells and occasional hyaline and granular casts per high power field.

*From the Department of Medicine, Jewish General Hospital, Montreal, Quebec.